Review

The paraoxonase 1, 2 and 3 in humans

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Abstract

The paraoxonase gene family in humans includes three members: *PON1*, *PON2* and *PON3*. The products of those three genes are the following enzymes: paraoxonase 1 (PON1), paraoxonase 2 (PON2) and paraoxonase 3 (PON3). PON1 is mainly associated with a high density lipoprotein (HDL). A small amount of this enzyme is also bound to very low-density lipoprotein (VLDL) and postprandial chylomicrons. PON1 possess organophosphatase, arylesterase and lactonase activity and it hydrolyzes many different substrates. It is also known that PON1 may have antiatherogenic function. Compared to the PON1, PON2 and PON3 are much less studied and described. PON2 is ubiquitously expressed intracellular protein, while PON3 is bound to HDL, like PON1. The both enzymes possess antioxidant properties.

Key words: paraoxonase 1; paraoxonase 2; paraoxonase 3

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Introduction

The genes *PON1*, *PON2* and *PON3* are the members of paraoxonase gene family in humans. These genes are located on the long arm of chromosome 7 and they are structurally similar. There is about 70% of identity in nucleotide sequences and about 60% of identity in amino acid sequences between these three genes. *PON1*, *PON2* and *PON3* have nine exons, however, *PON1* has an extra codon at the position 106 (lysine) in exon 4 which is not presented in *PON2* and *PON3*. From an evolutionary point of view and based on a structural homology, *PON2* is the oldest member of this gene family, followed by *PON3* and then by *PON1* (1-3). *PON1* mRNA is expressed in liver while *PON3* mRNA is expressed primarily in the liver but also in the kidneys. Unlike *PON1* and *PON3*, *PON2's* mRNA is ubiquitously expressed in different kinds of tissues like kidneys, liver, lungs, small intestine, placenta, spleen, stomach and testicles. *PON2* mRNA is also found in the cells of the artery wall, including endothelial cell, smooth muscle cell and macrophages (3).

The structure and function of paraoxonase 1

PON1 is a glycosylated protein consisted of 354 amino acid residues with an apparent mass of 43-47 kDa. Mature protein retains hydrophobic signal sequence on the N-terminal region, from which only the initiator methionine residue is removed (2,4,5). PON1 is synthesized in the liver, and then secreted into plasma where it is mainly bound to high density lipoproteins (HDL). The retained N-terminal signal peptide is essential for the association of PON1 with HDL. A small amount of PON1 was also detected in very low-density lipoprotein (VLDL) and postprandial chylomicrons (2,6).

PON1 possess organophosphatase, arylesterase and lactonase activities and hydrolyzes different kinds of substrates. PON1 hydrolyzes oxons like paraoxon, chlorpyrifos oxon and diazoxon which are toxic metabolites of organophosphate insecticides parathion, diazinon and chlorpyriphos. PON1 also hydrolyzes nerve agents like sarin and soman. In addition, PON1 hydrolyzes aromatic esters like phenylacetate, thiophenylacetate and 2-naphthylacetate and different aromatic and aliphatic lactones as well as cyclic carbonates like homogentisic acid lactone, dihydrocoumarin, γ-butyrolactone and homocysteine thiolactone. PON1 also catalyzes the reverse reaction, lactonization, of γ- and δ-hydroxy-carboxylic acids. Furthermore, PON1 participates in metabolism of some drugs which contain lactone and cyclic carbonates. For example, PON1 hydrolyzes the unsaturated cyclic carbonate prulifloxacin to the active quinolone antibiotic, diuretic spironolactone, and hydroxymethylglutaryl-CoA reductase inhibitors (mevastatin, lovastatin and simvastatin). In addition, it has been reported that PON1 has low levels of peroxidase and phospholipase A2-like activities (2,3,7-11).

Furthermore, it is well known that PON1 possess antiatherogenic activity, it protects HDL and low-density lipoprotein (LDL) from oxidation and destroys biologically active oxidized lipids on lipoproteins and in arterial cells (2,12,13). The endogenous substrate and the mechanisms of the antiatherogenic activity of this enzyme are still largely unknown. PON1 is traditionally named paraoxonase/arylesterase. Nevertheless, it was shown earlier in the text that PON1 catalyzes the formation and hydrolysis of different kinds of lactones. So it is assumed that the native activity of PON1 may be lactonase activity and that physiological substrate may be some lactones which are consumed as food ingredients, drug metabolites (statins, spironolactone and glucocorticoid γ-lactones) and derivatives of fatty acid oxidation process such as 5-hydroxy6E,8Z,11Z,14Z-eicosatetraenoic acid (5-HETE) lactone that resides in HDL (13).

PON1 has two calcium binding sites, the one is important for the stability of enzyme while the other one is important for the catalytic activity. The presence of calcium is required for the enzymatic activity and the removal of calcium with the chelating agents (like EDTA or EGTA) irreversibly destroys PON1's activity and stability (2,14). It was shown that many amino acids residues, like glutamine (E53, E195), aspartate (D54, D169, D183, D269, D279) histidine (H115, H134, H155; H243, H285) and tryptophan (W281) are important for organophosphatase and arylesterase activities. Furthermore, important amino acid residues of PON1 are the three cysteine residues at position 42, 284 and 353 (C42, C284, C353). C284 is free, while C42 and C353 form disulfide bond (2,15,16). C42 and C353 are important for secretion and catalytic activity of PON1. It was shown that the exchange of C42 or C353 with alanine resulting in inactivation and in decreased secretion of the enzyme (2,16). C284 was considered to be the active center nucleophile, however researches were showed that this amino acid residue is not specifically required for paraoxonase/arylesterase activity. The exchange of C284 with alanine or serine reduces paraoxonase/arylesterase activity but does not abolish these activities (2,17). It is assumed that C284 may be located close to the active center of the enzyme and it may participate in orientation or binding of the substrate (17). Furthermore, for the prevention of copper-induced LDL oxidation, calcium is not essential but C284 is required. On the basis of experimental data it may be concluded that PON1 has two catalytic sites, one responsible for hydrolytic activities, and the other one responsible for antioxidant activity. However, the existence of two catalytic sits has not yet been proved so Aviram and colleagues assumed that the two active sites of PON1 are overlapped (2,17).

Importance of HDL in secretion, stability and activity of PON1

The association of PON1 with HDL is necessary for maintaining the normal serum activity. The N-terminal hydrophobic signal peptide is the structural requirement for bounding of PON1 to this lipoprotein. HDL provides the optimal physiological acceptor complex which stimulates secretion and stabilizes the secreted enzyme. HDL also ensures amphypathic environment which protects the N-terminal hydrophobic region of enzyme and this environment may also be necessary for the interaction of PON1 with substrates (18,19).

The N-terminal sequence of PON1 is similar with signal sequence of secretor proteins. Cleavage of signal sequences in secretor proteins usually occurs in polar C-terminal flanking region. The amino acids at the positions -3 and -1 (usually small and uncharged residues) are critical for the cleavage of this sequence. In PON1 these positions are occupied with large and polar residues, histidine and glutamine, which prevent from the cleavage of this signal peptide (19). After a release from the cell, PON1 is bound at the HDL phospholipids through its N-terminal hydrophobic signal peptide. In that way, HDL assures hydrophobic shelter for the retained signal peptide in plasma's aqueous environment (18,19). James and colleagues presented a hypothetical scheme for HDL's mediated release of PON1 from cells in their article. HDL is bound on the cell membrane via scavenger receptor B1 (SR-B1). PON1, which was inserted into the external face of the cell membranes, is then transferred on HDL during transient association of the lipoprotein with cell (19).

PON1 is mainly associated with HDL, but this enzyme is also found on VLDL and postprandial chylomicrons, although to a lesser extent. However, PON1 is not associated with LDL (6). The majority of PON1 is associated with HDL which contains apolipoprotein AI (apo AI), while HDL which contains clusterin (apolipoprotein J) bound to approximately 30% of total PON1. Apo AI is not necessary for binding of PON1 on HDL, however it is important for the stability and activity of enzymes (20,21).

Total HDL in plasma presents a heterogeneous class of lipoproteins which has, a high density (>1.063 g/mL) and a small size (Stoke's diameter 5-17 nm) in common. By ultracentrifugal techniques HDL can be separated in two major subfractions; HDL_2 and HDL_3. HDL_2 is large, lipid rich and has a density range of 1.063-1.125 g/mL while HDL_3 is small, lipid poor and has a density range of 1.125-1.210 g/mL (22-24). Less than 10% of total HDL reacts with anti-PON1-antibodies which indicate that PON1 is not distributed across the entire HDL spectrum (19). The researches do not have a unique conclusion on the issue of association of PON1 with HDL_2 or HDL_3. It was assumed that PON1 follows the normal metabolic pathway of HDL. PON1 is bound to HDL_3, which enlarges and subsequently transforms into large HDL_2 during the accumulation of lipid components. Fractionation of HDL by gel filtration supports this assumption because PON1 was detected in larger size particles. Furthermore, when anti-PON1 immunoabsorbed column was used for the isolation of PON1-containing HDL particles, PON1 was detected on HDL_2 (19). Unlike these results, when ultracentrifugation was used for the separation of HDL fraction PON1 was detected on smaller sized HDL. A possible reason for the observed result is that the ultracentrifugation disrupts lipoprotein structure. During this procedure the peptides which are not tightly bound to HDL, can be stripped off and accumulated in very high density particles or even in the lipoprotein free fraction of plasma. So it is possible that PON1 is redistributed during the ultracentrifugation. (19,24-26). If the method of selective precipitation is used, the majority of PON1 is located in HDL_3 fraction (27).

The non-genetic factors which affect PON1's activity

PON1's activity and its concentration in serum show large inter-individual variability. PON1's concentration varies up to 13 times, while PON1's activity can vary up to 40 times. Different genetic factors, polymorphisms in promoter and coding region of the *PON1* gene, together with different non-genetic factors, both affect PON1's activity and concentration (2,20,28-30).

Diets rich with *trans*-unsaturated fat and meals rich in used cooking fat, which contains a high content of oxidized lipids reduce PON1's activity. On the other hand, the oleic acid from olive oil increases PON1's activity. The consumption of pomegranate juice rich with polyphenols and other antioxidants, results in higher PON1's activity. However, the effect of antioxidant on PON1's activity requires further research because of discrepancy in the obtained results. The conducted researches have showed positive and negative correlation between, for example the consumption of vitamin C and E or even no association between the intake of vitamin C, E and β-carotene with PON1's activity (20,29,30). Moderate alcohol consumption (bear, red wine and spirits) results in increased PON1's activity and concentration. There were no differences between red wine, bear and spirits so it was suggested that the red wine polyphenols alone are not responsible for this effect. Moderate consumption of alcohol drinks increases the concentration of HDL and apo AI which may result in observed rise of the enzyme's concentration. However, some results did not show association between alcohol consumption and PON1's activity (20,29,30).

The activity and concentration of PON1's in serum is lower in smokers than in non-smokers. Ex-smokers have PON1's activity and concentration similar to those found in non-smokers, which indicates a reversible effect of smoking on PON1. It was also shown that moderate alcohol consumption or regularly exercise can attenuated the effect of smoking on PON1 so that the observed levels of PON1 in this population are similar to those by non-smokers (20,29,30).

Furthermore, exposure to the environmental toxins affects PON1's activity. For example, the exposure to organophosphate or the exposure ionizing radiation results in decrease of PON1's activity (20,29,31,32).

Aging also affects PON1's activity. The serum activity after birth is very low, and then it rises and achieves the values as in adults between 6 and 15 month of age. Once it reaches the adults' values, PON1's activity is relatively constant during life time. However, a progressive decrease is detected by elderly subjects (20,29).

Different physiological conditions affect on PON1's activity, for example pregnant women have a reduced activity. Furthermore, PON1's activity can vary depending on different pathological condition. Lower PON1's activity was observed in patients with insulin-dependent diabetes and non-insulin-dependent diabetes, in patients with chronic renal failure undergoing haemodialysis, in patients with rheumatoid arthritis, hyperthyroidism, Alzheimer's disease and chronic liver disease. Reduced PON1's activity is also related to insulin resistance, high serum cholesterol and inflammation (20,29,31,32).

Polymorphisms in coding region of *PON1* gene

More than 160 polymorphisms were identified in regulatory, intron and coding regions of *PON1* gene. It is known that some of this polymorphisms affect the PON1's concentration and activity (20,29).

Two polymorphisms in the coding region of *PON1* gene have been thoroughly studied. In Q192R polymorphism, the exchange of codon CAA to CGA in exon 6 of *PON1* gene results in substitution of amino acid glutamine with arginine at the position 192. In L55M polymorphism, the exchange of codon TTG to ATG in exon 3 of *PON1* gene results in the substitution of amino acid leucine to methionine at the position 55 (33). Q192R have been more widely studied out of these two polymorphisms, because the Q192 and R192 alloenzymes have a different affinity and catalytic activity towards numerous substrates (20). The R192 alloenzyme hydrolyzes paraoxon six times faster than Q192 alloenzyme. On the other hand, the Q192 alloenzyme hydrolyzes sarin, soman and diazoxon faster than R192 alloenzyme (7,20). These two alloenzymes are also different in hydrolysis of some lactones and carbonate esters. For example, hydrolyze of angelicolactone and δ-valerolactone is faster with Q192 alloenzyme, while R192 alloenzyme hydrolyze faster, for example, thiolactones and γ-butyrolactone. Furthermore, there are no differences in hydrolysis rate for the same substrates, for example for phenylacetate (7,8,20). Q192R polymorphism also affects on enzyme's ability to protect LDL from oxidation *in vitro*, while Q192 alloenzyme is more efficient than R192 aloenzyme (17,20,34,35).

In vitro experiment showed that R192 alloenzyme is much more protective against the toxic effect of paraoxon, while Q192 alloenzyme provides more protection against the toxic effect of diazoxon. But, *in vivo* experiment on PON1-knockout mice which received the same amount of either Q192 or R192 alloenzyme, showed that both alloenzyme provide the same protective effect against diazoxon. Furthermore, R192 alloenzyme provides more protection against chlorpyrifos oxon *in vivo*, and the same effect was observed *in vitro*. Neither of these two alloenzymes showed protective effect against paraoxon *in vivo*. It can be concluded that PON1 plays a major role in the detoxification of diazoxon and chlorpyrifos oxon, but not paraoxon *in vivo* (36).

It was shown earlier that arginine at the position 192 is an important amino acid residue of enzyme's active centre, which can explain the differences in enzyme activity of these two alloenzymes towards different substrates (20,37).

L55M polymorphism does not affect interaction of the enzyme with substrates, but affects PON1's mRNA levels and the concentration and activity of PON1. M55 alloenzyme is related to the lower enzyme's activity and concentration and to the lower level of PON1's mRNA (20,38,39,40). These two alloenzymes are also different in protections of LDL against oxidation, where M55 alloenzyme shows to be more protective (34,35). It was shown that L55M polymorphism is in strong linkage disequilibrium with polymorphisms in the promoter region of *PON1* gene, which influences PON1's expression and activity. It was considered that the connection of L55M polymorphism to variation in PON1's concentration is a consequence of the observed linkage disequilibrium. However, some later researches showed that the linkage disequilibrium does not provide the complete explanation of L55M polymorphism's effect on enzyme's concentration. Independently from -108C>T polymorphism in the promoter region of *PON1* gene, subjects caring LL genotype were had a higher PON1's concentration than the individuals with MM genotype (20,41,42). L55 alloenzyme is more stabile and resistant to proteolysis, which can partly explain the association of this alloenzyme with higher concentration of PON1 in serum. The analysis of crystal structure showed that L55 alloenzyme has a key role in the correct packing of the protein (20,37,42).

Some other polymorphisms in the coding region of *PON1* gene were found, however these polymorphisms are not yet thoroughly studied. For example, the exchange of isoleucine with valine at the position 102 in Finnish and the exchange of arginine with glycine at the position 160 in Chinese (43,44).

The polymorphisms in the promoter region of *PON1* gene

At least five polymorphisms which are located on position -909 (G or C), -832 (A or G), -162 (A or G), -126 (C or G) and -108 (C or T) when the base immediately preceding the start codon is numbered as "-1", have been identified in the promoter region of *PON1* gene. The nomenclature differences for these polymorphism which occur in literature (-107/-108, -160/-162, -824/832 and -907/-909) are likely due to the small variations in the sequences examined by the different researches' groups. Leviev and co-workers affirmed that -108 and -832 polymorphisms have an influence on *PON1* expression, while -909 polymorphism does not affect the gene expression (41). Furthermore, Brophy and colleagues found that the -108, -162 and -909 polymorphisms affect, while -832 and -126 polymorphisms do not affect *PON1* expression. The differences in the observed results could be a consequence of the interactions among the polymorphisms resulting in the context effects (47). -108C, -832A, -162A and -909G have higher levels of expression than -108T, -832G, -162G and -909C. The variation in promoter activity are physiologically relevant since they are correlated to significant differences in serum concentration and activity of PON1 (20,41,45-47). The analysis of each polymorphism's individual contribution in the promoter region of *PON1* gene on PON1's concentration and activity, is complicated because of linkage disequilibrium between them and between Q192R and L55M and the promoter region polymorphisms (2,20,41,46). It is believed that -108C>T polymorphism is the main contributor to variation of PON1 in serum which explain approximately 23-24% of the total variation, while -162A>G, -909G>C and -832A>G have a small or no effect on PON1's level (20,46). The part of promoter region of approximately 200 bp which contains the polymorphic positions -108 and -162 is sufficient for transcription of *PON1* gene (20). Because -108C>T polymorphisms seems to have the highest effect on PON1's variation in serum, this polymorphisms has been thoroughly studied. This polymorphism is located in the centre of a consensus' binding site for the ubiquitous transcription factor Sp1 (specific protein Sp1). Presence of T at the position -108 disrupts the sequence which recognizes Sp1 and the binding of this factor is weaker in the presence of T than C. The promoter activity in the case of -108T is significantly lower than in the case of -108C but it is present, indicating that this region is only partly regulating the *PON1* transcription. Out of all the promoter polymorphisms, beside -108C>T, only -162A>G polymorphism is located within sequences for transcription factor. The polymorphic position -162 is located in a consensus binding site for the NF-1 (nuclear factor-1). The presence of G at the position -162 disrupts the sequence of the binding site resulting with lower gene expression (2,20,41,45-48). The polymorphisms have been identified in 3'-untranslated region of *PON1* gene, however, the significance of these polymorphisms is not yet studied (2,46).

The distribution of *PON1* gene polymorphisms in population

The frequency of Q192R and L55M alleles are different among populations. The Caucasian population has a higher frequency of Q192 and L55 alleles while the Asian population has a higher frequency of R192 allele and a very low frequency of M55 allele. Caucasian population of North America have frequency of Q192 allele 0.70-0.72 and L55 allele 0.64 and Caucasian population of Europe have frequency of Q192 allele 0.67-0.74 and L55 allele 0.57-0.64. Asian population of China have frequency of Q192 allele 0.36-0.43 and L55 allele 0.96 furthermore Asian population of Japan have frequency of Q192 allele 0.38-0.41 and L55 allele 0.91-0.94. The frequency of -108C and -108T allele is not different between these two populations. The frequency of -108C allele is 0.5 for Caucasian population of North America, 0.46 for Caucasian population of Europe and 0.48 for Asian population of Japan (2,46,49).

PON1 phenotype and *PON1* status

PON1's phenotype is determined with genetic factors, polymorphisms of *PON1* gene, and different non-genetic factors which affect PON1's activity. Paraoxonase PON1's activity show bimodal distribution and allows the separation of phenotype AA (homozygote low activity) from phenotypes AB (heterozygote) and BB (homozygote high activity). The method using two substrates is most widely used today, and allows separation of all the three phenotype. Eckerson and co-workers described a method in which substrates paraoxon and phenylacetate were used for determination of PON1's phenotype. Unlike the bimodal distribution of paraoxonase activity, arylesterase activities show unimodal distribution and ratio of paraoxonase/arylesterase activities is trimodal. The ratio of these two activities allows separation of all the three phenotypes: AA, AB and BB. Two alloenzymes of PON1 have a different turnover number for paraoxon and a similar turnover number for phenylacetate (2,50,51). The molecular background of polymorphic distribution of paraoxonase PON1's activity is the Q192R polymorphism. Humbert and co-workers identified that the individuals with B alloenzyme have arginine at the position 192, while the individuals with A alloenzyme have glutamine at this position. The phenotype AA matches with the genotype QQ, the phenotype AB with the genotype QR and the phenotype BB with the genotype RR (52). Since arylesterase activity does not have polymorphic distribution, this activity served for the estimation of PON1's concentration in serum. The arylesterase activity correlates with PON1's concentration independently from genotypes of Q192R polymorphism, while paraoxonase activity correlates with PON1's concentration only within the certain genotype of this polymorphism (53-56). For the determination of PON1 phenotype other substrates can be used instead of substrate phenylacetate, like chlorpyrifos oxon or diazoxon together with substrate paraoxon. The best distinction of PON1's phenotype was achieved with substrates paraoxon and diazoxon (2,56).

There is a wide variation in PON1's concentration and activity between individuals even within genotype groups. The epidemiological studies which analyze the correlation of PON1 with different pathological condition should include the determination of polymorphisms together with PON1's status (20). PON1's status provides a functional assessment of the PON1's 192 alloforms and also provides the plasma level of PON1 for the each individual. Although polymorphisms in *PON1* gene have the greatest effect on PON1 status, different non genetic factors also effect PON1's concentration and activity and contribute to the enormous interindividual variation. PON1's status can be determined by the measuring concentration and enzyme's activity or by using the method with two substrates. The two-dimensional enzyme analysis utilizing paraoxon and diazoxon provides the best determination of PON1 status (20,29,56-59).

Paraoxonase 2 and paraoxonase 3

In contrast to PON1, PON2 and PON3 enzyme are much less studied. PON2 is an intracellular protein with relative molecular mass of approximately 44 kDa (3). PON2 mRNA is expressed in almost all human tissues, with the highest expression in liver, lungs, placenta, testicles and heart. PON2 mRNA is also found in the cells of the artery wall, including endothelial cell, smooth muscle cell and macrophage. PON2 is not associated with HDL or LDL (3,49). Although, PON2 has the N-terminal signal sequence like PON1 and PON3 it appears that it is located in the cells associated with the plasma membrane. It is considered that only a small amount of PON2 is secreted from the cell or that the enzyme may be rapidly degraded following secretion (3,60). PON2 has got antioxidant properties, lowers the intracellular oxidative stress and prevent the cell-mediated oxidation of LDL. Ng and coworkers was demonstrated that the cell which overexpress PON2 oxidatively modify LDL to a lesser extent. PON2 not only prevents from the oxidation modification of LDL, but is also able to reverse the oxidation of minimally modified LDL (mmLDL). LDL and mmLDL which was incubated with cells that overexpress PON2 have significantly lower levels of lipid hydroperoxides and are less able to induce monocyte chemotactic activity than LDL and mmLDL incubated with control cells. The overexpression of PON2 also decreases the oxydative stress in the cells which were treated with hydrogen peroxide or oxidized phospholipids. Since PON2 is a ubiquitously expressed intracellular protein, it is most likely that PON2 plays a role in the reduction of intracellular or local oxidative stress (3,31,49,60). Two common polymorphisms were identified at the positions 148 and 311 in the *PON2* gene and both polymorphisms lead to amino acid substitution. Alanine or glycine could be at the position 148 (A148G) while serine or cysteine could be at position 311 (S311C). A148G polymorphism is related for example with variation of total and LDL cholesterol, with fasting plasma glucose levels and with birth weight. S311C polymorphism has been related for example with coronary artery disease, ischemic stroke in patients with type 2 diabetes mellitus, Alzheimer's disease and reduced bone mass in postmenopausal women (3,31,49).

Out of all the three PON enzymes, PON3 was discovered the last. PON3 is primarily synthesized in the liver and is associated with HDL in serum but in much lower levels than PON1. Beside in the liver PON3 mRNA expression was also detected in the kidney. PON3 has molecular mass of approximately 40 kDa and has also got the antioxidant properties. It was shown that PON3 prevent the formation of mmLDL and inhibits mmLDL induced monocyte chemotactic activity (3,31,49,61). The two polymorphisms, at the position 311 and 324, were identified in *PON3* gene. At the position 311 is serine or threonine and at the position 324 is glycine or aspartic acid. These polymorphisms were detected within the population of southern Italy but the functional consequences of these polymorphisms have not been reported (3).

In contrast with PON1, PON2 and PON3 lack, or have very limited paraoxonase and arylesterase activities, but the both enzymes hydrolyze aromatic and long-chain aliphatic lactones like dihydrocoumarin. PON3 hydrolyzes some drugs like statin lactones (lovastatin and simvastatin) and a diuretic spironolactone (2).

Conclussion

It is well known that PON1, PON2 and PON3 have antioxidant function, but differences in enzyme's activity and localization indicate that these tree enzymes have got different functions in the human body. However, all the three enzymes share an ability to hydrolyze different kinds of lactones. PON1's activity and its concentration in serum show large inter-individual variability (62) and its physiological function and physiological substrate still remains unknown. Further well designed studies must be conducted to identify its natural substrates and the mechanisms of catalytic and antiatherogenic activity.

Potential Conflicts of Interest: None declared.

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Humana paraoksonaza 1, 2 i 3

Sažetak

Humanu porodicu *PON* gena čine tri člana: *PON1*, *PON2* i *PON3*. Produkti ove porodice gena su enzimi paraoksonaza 1 (PON1), paraoksonaza 2 (PON2) i paraoksonaza 3 (PON3). PON1 je najvećim dijelom vezan na lipoprotein velike gustoće (HDL). Manja količina PON1 vezana je i na lipoprotein vrlo niske gustoće (VLDL) te na postprandialne hilomikrone. PON1 posjeduje organofosfataznu, arilesteraznu i laktonaznu aktivnost te hidrolizira različite vrste supstrata. Također je poznato da PON1 posjeduje i antiaterogeno djelovanje. Za razliku od PON1, enzimi PON2 i PON3 su manje detaljno opisani. PON2 je unutarstanični protein dok je PON3 poput PON1 vezan na HDL. Oba eznima posjeduju antioksidacijsko djelovanje.

Ključne riječi: paraoksonaza 1; paraoksonaza 2; paraoksonaza 3